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Time spent in rehabilitation and effect on measures of activity after stroke (Protocol)

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[Intervention Protocol]

Time spent in rehabilitation and effect on measures of activity after stroke

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

- To establish if greater time spent in rehabilitation results in greater improvement in measures of activity than less time spent in rehabilitation.
- To assess the effect of total time spent (in minutes) in rehabilitation on activity/activity limitations following stroke.
- To assess the effect of rehabilitation schedule on activity/activity limitations following stroke in terms of:
    - average minutes of rehabilitation provided per week;
    - average frequency of rehabilitation provided per week;
    - total duration of rehabilitation.

- average minutes of rehabilitation provided per week;
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- total duration of rehabilitation.

BACKGROUND

This review will explore the effect of time spent in rehabilitation after stroke. We acknowledge that 'time spent' is potentially an ambiguous term. For the purpose of this review, we consider 'time spent' to include

- the number of minutes of rehabilitation provided, per week;
- the frequency of rehabilitation provided per week (i.e. number of days per week on which rehabilitation was provided);
- the time-period over which rehabilitation was provided, or rehabilitation duration.

The outcome of rehabilitation after stroke may also be affected by how these different elements are combined. For example, the outcome of a certain number of minutes of rehabilitation provided over a shorter time-period may be different to the same number of minutes provided over a longer time-period. We acknowledge that, to some, 'time spent in rehabilitation' could be synonymous with 'rehabilitation intensity'. Whilst the term 'intensity' could be used to describe the time-related elements described above, it has also been used to describe alternative characteristics of rehabilitation, including number of repetitions performed within treatment sessions (Scrivener 2012) and physiological effort exerted (Outermans 2010). We will not explore these characteristics in this review. Other terms to describe 'time spent in rehabilitation' could be 'dose of rehabilitation' or 'amount of rehabilitation'.

Description of the condition

Stroke is a "neurological deficit attributed to an acute focal injury of the central nervous system by a vascular cause" (Sacco 2013). It is a significant, global health issue. In 2010, there were approximately 16.9 million first-ever strokes and 33 million stroke survivors worldwide (Feigin 2014). Stroke is one of the leading causes of disability (Adamson 2004). In 2010, 102 million disability adjusted life years (DALYs) were lost after stroke (Feigin 2014). In the UK alone, over 27,000 (37%) of people discharged from hospital from April 2013 to March 2014 required help with activities of daily living such as washing and dressing (Royal College of Physicians 2014). Such disability results in significant cost due to care requirements and loss of productivity (Mozaffarian 2015; Saka 2009). Better rehabilitation outcomes after stroke would reduce the impact of disability and dependence on the quality of life of people with stroke and their carers (Nichols-Larsen 2005), and national economies (Truelsen 2005).

Description of the intervention

Stroke rehabilitation is a broadly-based, multi-dimensional process encompassing interventions that aim to facilitate restitution or substitution of limitations in impairment, activity, or participation caused by stroke (Dobkin 2005; NICE 2013). According to Langhorne 2011, rehabilitation after stroke typically follows a four-stage, cyclical process of assessment of need, goal setting, intervention, and reassessment.

Previous Cochrane Reviews have explored various different rehabilitation interventions for various different outcomes after stroke. Interventions have included physical rehabilitation (Pollock 2014a), cognitive rehabilitation (Bowen 2013; Chung 2013; das Nair 2016; Loetscher 2013), telerehabilitation (Laver 2013), virtual reality (Laver 2015), acupuncture (Yang 2016), electromechanical and robot-assisted arm training (Mehrholz 2015), mirror therapy (Thieme 2012), physical fitness training (Saunders 2016), motivational interviewing (Cheng 2015), constraint-induced movement therapy (CIMT) (Corbetta 2015), repetitive transcranial magnetic stimulation (Hao 2013), and repetitive task training (French 2007). Whilst there is value in determining the efficacy of specific rehabilitation interventions, it is acknowledged that, in practice, the content of rehabilitation therapy is not clearly defined and varies between both therapists and services (Ballinger 1999; DeJong 2005). The relationship between type of therapy and response is unclear (Lohse 2014), with therapists adopting an eclectic approach (Jette 2005). Therefore, this review is adopting an 'intervention agnostic' approach, seeking to explore not if one type of rehabilitation is superior to another, but to explore the specific effect of time spent in rehabilitation.

In the Cochrane Review of 'Physical rehabilitation approaches for the recovery of function and mobility following stroke', Pollock 2014a identified that rehabilitation could be provided by a variety of professions. This included therapists, therapists with assistance from family members, physiotherapists, rehabilitation nurses, nurses, occupational therapists, doctors, sports therapists, student physiotherapists, and research physiotherapists. This review is not limited to any specific provider of rehabilitation but acknowledges that, in many countries and healthcare systems, therapists provide rehabilitation. Therefore, for the purpose of this review, we will refer to providers of rehabilitation as therapists.

This review is not limited to physical rehabilitation following stroke, but any rehabilitation intervention, where time spent in rehabilitation is greater than zero. As we are interested in exploring the effect of time spent in rehabilitation on measures of activity after stroke, we are primarily interested in rehabilitation interventions that target this level of recovery. This will be determined by studies that use activity level outcome measurements. For the purpose of this review, therefore, we define rehabilitation as any non-pharmacological, non-surgical intervention that aims to improve activity after stroke.

How the intervention might work

In this review, the intervention is any non-pharmacological, non-surgical intervention that aims to improve activity after stroke and the influence of time spent on intervention. These interventions might work through neuroplasticity: the brain's ability to modify neuronal activity and reorganise neural connections. Neuroplasticity underpins both recovery of and compensation for impaired motor function after stroke (Buma 2013; Dobkin 2005; Kleim 2008; Levin 2009; Nudo 2013). The differentiation between recovery, where survivors initially regain their pre-morbid kinematic/muscle activation patterns and compensation, where alternative kinematic/muscle activations are used to accomplish a task is thought to occur by around the first five to eight weeks after stroke (Kwakkel 2015; Van Kordelaar 2013).

Research points to many potentially important aspects of stroke rehabilitation that will influence outcomes. Kleim 2008, in their review of the evidence for experience-dependent neural plasticity, identified that repetition, the relative importance of the task undertaken, and skill acquisition (as opposed to simply use) will influence plasticity. Other authors described further important aspects in the re-learning of motor skills, such as the use of explicit versus implicit learning (Boyd 2003; Boyd 2004). The presence of a meaningful context or goal has been shown to enhance motor learning (Ma 1999; Wu 2000). There is evidence that extrinsic feedback enhances motor-learning after stroke (Van Vliet 2006) and that stroke survivors benefit more from random practice of exercise than they do block practice (Hanlon 1996). Wulf 2010 discussed additional influences on learning, such as learning through observation, and internal versus external focus of attention and self-controlled practice. Mount 2007 discussed research related to the impact of errorless learning versus trial and error learning, whilst Levack 2006 suggested that specific, difficult goals may enhance performance. Finally, research suggests that an enriched environment enhances recovery post-stroke (Janssen 2010).

The purpose of this review, however, is to explore the effect of the time spent in rehabilitation for activity level outcomes after stroke. Whilst it is acknowledged that other factors will influence outcomes, we assume that these other factors are similarly distributed in an intervention where only the time spent in rehabilitation is the variable of focus for this review.

Mechanistically, one type of learning that promotes neuroplasticity is Hebbian Learning (Hebb 1949). Hebbian (and anti-Hebbian) Learning is concerned with an increase in synaptic efficacy, due to repetitive firing of the pre-synaptic cell, causing stimulation of the post-synaptic cell, leading to increased synaptic strength (Nudo 2013). Evidence indicates that repetition is key to increasing synaptic efficacy (Kleim 2008; Nudo 2013). From a therapist's perspective, then, it could be interpreted that the time spent in rehabilitation may determine the frequency of synaptic stimulation and therefore more time spent in repetitive rehabilitation should increase synaptic strength.

As Nudo notes, behavioural experience, or the intervention itself, is one of the most important factors in the modulation of cortical function and structure (Nudo 2013). Behaviourally, there is a large body of evidence regarding motor learning (and re-learning) in non-disabled people (Wulf 2010) and also in people with stroke (Kitago 2013) where the main principles of repetition, 'just right' challenge (Guadagnoli 2004) and graded feedback (Winstein 1990) closely align with the key principles of neuroplasticity (Kleim 2008), again supporting the premise that increased time spent in rehabilitation will provide more beneficial change in the performance outcomes of a task.

Several intervention studies also suggest that the time spent in rehabilitation after stroke is more important than the type of rehabilitation. A narrative review of CIMT found that CIMT compared with dose-matched bilateral arm training did not produce significant differences in overall effect sizes (Kwakkel 2015). Phase 2 and 3 randomised controlled trials (RCTs) have found no significant differences in outcomes between CIMT and dose-matched 'traditional occupational therapy' (Dromerik 2009), robot-assisted therapy and dose-matched intensive therapy (Lo 2010), or structured task-oriented training and dose-equivalent usual care (Winstein 2016). Taken together, these and similar findings indicate that, as long as the rehabilitation provided is of equal amounts, it does not matter very much what type or content of therapy is given. This has led to many studies comparing amounts of therapy for a given population as the factor of interest (as reviewed in a later section). However, 'more is better regardless' is almost certainly an oversimplified view of how rehabilitation interventions might work.

For example, in the recent ICARE study (Winstein 2016), a usual-care low-dose group did as well as the two higher-dose-matched groups at the one-year end-point suggesting that dose of rehabilitation may not be the most important factor in recovery levels measured long after the intervention, although the three groups are confounded by having different types of intervention. Furthermore, Dromerik 2009 found that providing a greater dose of CIMT, when given early after stroke, had a detrimental effect on outcomes related to activities of daily living. This suggests that time spent in rehabilitation interacts with stage of recovery and spontaneous recovery processes. These two studies both suggest that timing of an intervention may be important. A study in the chronic population, comparing bilateral rhythmic arm training and unilateral dose-matched therapeutic exercises, determined that the two interventions did not operate through the same neuroplastic mechanisms, despite eliciting similar outcomes at the impairment and activity level (Whitall 2011). This finding indicates that type of rehabilitation and what the rehabilitation targets interacts with the underlying mechanisms in ways we do not completely understand yet.

Finally, all of the intervention studies above have the problem of how to actually dose-match different types of rehabilitation so that they are truly equivalent in effort by the patient at any given amount. This is an almost impossible task, which, given this problem as well as the evidence just presented that the type of intervention may well be important after all, leads us to question whether it is valid to compare different amounts of time spent in rehabilitation with two different interventions. We pursue this point further below.

In summary, it is thought that rehabilitation interventions 'work' by influencing the recovery from and compensation for the neurological damage caused by stroke. The time spent in rehabilitation may be a factor in determining the effectiveness of this intervention for reducing activity limitation.

Why it is important to do this review

The effect of time spent in rehabilitation post-stroke has been explored extensively in the literature, but without clear conclusions. A meta-analysis that combined outcomes showed positive results (Lohse 2014). Other meta-analyses have found in favour of increased time spent in rehabilitation (in terms of total amount or daily minutes) for walking speed (Cooke 2010; Kwakkel 2004; Veerbeek 2011). However, by contrast, Galvin 2008 found no significant beneficial effect for increased time spent in rehabilitation (in terms of total amount) of exercise therapy for walking speed.

The effect of increased time spent in rehabilitation on activities of daily living (ADLs) is also uncertain. Some meta-analyses exploring this relationship have found in favour of an increased amount of time spent in rehabilitation (in terms of total amount or daily minutes) for ADL outcomes (Galvin 2008; Kwakkel 2004; Veerbeek 2014). However, Veerbeek 2011 found a non-significant summary effect size (standard mean difference (SMD) 0.11, P = 0.36) for basic ADLs (such as personal care), but a significant, medium summary effect size (SMD 0.54, P = 0.002) for extended ADLs (such as domestic activities and community access). In addition, it is unclear if more rehabilitation is beneficial for upper limb recovery. Cooke 2010 found additional rehabilitation beneficial for upper limb muscle function, but Kwakkel 2004 found no effect for dexterity.

The suggestion that increased time spent in rehabilitation may produce favourable outcomes has led to the following recommendations.

- The National Institute of Health and Care Excellence guidance for long-term rehabilitation after stroke recommends a minimum 45 minutes of each relevant rehabilitation therapy (occupational therapy, physiotherapy, and speech and language therapy), five days per week (NICE 2013).

- The Canadian Best Practice guidelines for rehabilitation states that patients should receive a minimum of three hours of task-specific therapy, five days per week, delivered by an interprofessional stroke team (Dawson 2013).

- The Australian Stroke Foundation, Clinical Guidelines for Stroke Management states that a minimum of one hour of active practice of physical therapy (occupational therapy and physiotherapy) should be provided at least five days per week (National Stroke Foundation 2010).

These guidelines all suggest minimum daily session duration (in terms of hours/minutes of rehabilitation that should be provided) and a suggested frequency of rehabilitation (in terms of day per week) that rehabilitation should be provided. They do not all make a recommendation for treatment duration (in terms of the length of time over which rehabilitation should continue).

The published literature does not provide a clear evidence base for these guidelines (Cooke 2010; Galvin 2008; Kwakkel 1997; Kwakkel 2004; Langhorne 1996; Lohse 2014; Veerbeek 2011; Veerbeek 2014). These meta-analyses include 71 unique studies. In at least 50 of these studies, the experimental and control interventions differed in not only the amount of rehabilitation provided, but also the type of rehabilitation provided. For example, a study by Sivenius 1985, included in five of the aforementioned meta-analyses, compared stroke survivors treated in a specialist stroke rehabilitation unit to those treated in the medical wards of the local University Hospital. Whilst those in the stroke rehabilitation unit received a greater amount of rehabilitation, the difference in location may have also contributed to the difference in outcomes. Another example is Smania 2012, which compared a less intensive CIMT (and therefore described as modified CIMT - mCIMT) to "conventional therapy". As previously mentioned, it may be that type of rehabilitation influences outcomes, as well as amount of time spent in rehabilitation. Arguably, therefore, conclusions regarding the effect of amount should not be drawn from studies comparing different types of rehabilitation.

Two meta-analyses explore the "optimum amount" of rehabilitation post-stroke. Kwakkel 2004 used a cumulative meta-analysis and, although their findings did not support a precise optimal amount of time spent in rehabilitation, no ceiling effect was found. Lohse 2014 used meta-regression to explore the effect of total scheduled therapy time on effect sizes. They found a potentially non-linear relationship between total amount of therapy and outcomes. This suggests that there may be an 'optimal amount' of therapy time, beyond which the benefits of additional therapy are limited. Taken together, these meta-analyses suggest that guidelines that include a specific minimum amount of rehabilitation are pragmatically-based, as opposed to evidence-based.

Currently, there is a Cochrane Review published that explores the effect of repetitive task training on functional ability after stroke (French 2007). In addition, there is a Cochrane protocol published that plans to explore the effect of additional exercise therapy after a stroke (Galvin 2012). In their Cochrane Review 'Physical rehabilitation approaches for the recovery of function and mobility following stroke', Pollock 2014a undertook a subgroup analysis exploring the effect of dose of physical rehabilitation on functional recovery and the recovery of motor function after stroke. In addition, Pollock 2014b undertook a Cochrane Review of interventions for improving upper limb function after stroke. This review identified the need for evidence related to dose of intervention, in order to inform future research and clinical practice. Finally, a Cochrane Review by Brady 2016 included an analysis on 'intensity' of speech and language therapy (expressed in number of hours per week spent in therapy) for aphasia after stroke. As yet, there is no Cochrane Review exploring the effect of time spent in rehabilitation on activity after stroke. We consider our review important in order to determine if the increasing number of clinical guidelines that recommend a specific minimum amount of time spent in rehabilitation after stroke have an evidence base and therefore, may be important for future guideline development. Based on current guidelines and evidence there is also a strong push for technologies that enable additional practice, especially in the home and without additional therapist support. A better understanding of the importance of amount of time spent in rehabilitation will inform development of new technologies such as telerehabilitation and use of virtual reality.

OBJECTIVES

- To establish if greater time spent in rehabilitation results in greater improvement in measures of activity than less time spent in rehabilitation.
- To assess the effect of total time spent (in minutes) in rehabilitation on activity/activity limitations following stroke.
- To assess the effect of rehabilitation schedule on activity/activity limitations following stroke in terms of:
    - average minutes of rehabilitation provided per week;
    - average frequency of rehabilitation provided per week;
    - total duration of rehabilitation.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised trials that compare different amounts of time spent, greater than zero, of the same rehabilitation intervention. These may be RCTs (participants are randomised to either an experimental group or a control group) or randomised clinical trials (participants are randomised to different experimental groups). We will also include data from the first period of randomised cross-over trials. We will include cluster-randomised trials should we find any. We have restricted the types of studies to randomised trials only, as they are considered to be high-quality sources of evidence in clinical practice (Devereaux 2003) and the method by which causality can be established (Concato 2010; Horn 2005; Kersten 2010).

Types of participants

Participants will be adults (over 18 years), with a clinical diagnosis of stroke, caused by either infarct or haemorrhage (including subarachnoid haemorrhage). Participants will have received rehabilitation either in an inpatient, outpatient, or community setting. We will exclude studies that also include participants with diagnoses other than stroke as the primary diagnosis.

Types of interventions

We will include trials that compare different amounts of time, greater than zero, spent in rehabilitation. For the purpose of this review, this will be defined as any non-pharmacological, non-surgical intervention that aims to improve activity after stroke.
As discussed in the Background, there are many different types of rehabilitation intervention and many different aspects of stroke rehabilitation that may affect outcome. To establish if time spent (in terms of minutes, frequency and duration) is related to outcomes, studies included must vary only in the amount of time spent in rehabilitation between the experimental and the control conditions. If studies include more than one treatment arm, one of which meets the criteria for this review, we will include the control group and intervention arm that is compliant with the criteria for this review. If the control group of any study receives no treatment, then we will exclude the study.
Co-interventions will not preclude inclusion, provided they are administered to both experimental and control groups.

Types of outcome measures

The International Classification of Functioning, Disability and Health (ICF) aims to provide a framework for the description of health and health-related status (WHO 2001). Although published in 2001, the ICF is updated regularly. An application of the ICF is to classify the measurement of outcomes (WHO 2001). The ICF classifies the components of functioning and disability as: 1) body structures/body functions and potential impairments at this level; 2) activity and potential activity limitation; and 3) participation, the involvement in life tasks and the potential restrictions an individual may experience.
We will include published outcome measures falling into ICF categories for activity and body structures/body functions. We are primarily interested in measures of activity, as these outcomes are likely to be most meaningful to stroke survivors and to indicate a reduction in the burden of care. We are also interested in measures of body structure/body function, as they will indicate if an increased amount of time spent in rehabilitation facilitates recovery at this level. We will not include outcome measures in the participation category, as these outcomes are likely to be attributable to factors other than rehabilitation.

Primary outcomes

We will define the primary outcome measures for this analysis as ADL outcomes (an activity measure). We will include any measure of ADL, including but not limited to (and in no specific order): Barthel Index, Frenchay Activity Index, Rivermead ADL Assessment, Nottingham Extended ADL, Functional Independence Measure.

As we plan to pool these outcome measures, if studies have utilised more than one measure of ADL, we will select the measure for which they have collected the most data, in order to avoid double counting. If there are measures with equal amounts of data in a study, we will select the measure listed first in the study.

Secondary outcomes

1. Activity measures of the upper limb (e.g. Action Research Arm Test, Jebsen Taylor Hand function Test)
2. Activity measures of the lower limb (e.g. timed up-and-go, 6-minute walk test, walking speed and the Rivermead Mobility Index)
3. Motor impairment measures of the upper limb (e.g. Fugl-Meyer assessment, muscle strength, range of movement)
4. Motor impairment measures of the lower limb (e.g. muscle strength, range of movement)
5. Serious adverse events/death
6. Participant experience

As for the primary outcome measure, we plan to pool the measures used, within each secondary outcome. If studies have utilised more than one measure relevant to that secondary outcome, we will select the measure for which they have collected the most data, in order to avoid double counting. If there are measures with equal amounts of data in a study, we will select the measure listed first in the study.

We will exclude any studies that have not used any of the primary or secondary outcome measures described above.

For all outcome measures, we are primarily interested in measures taken immediately after intervention. However, we will also undertake analysis of medium-term outcomes (two weeks to six months after treatment has ended) and long-term outcomes (more than six months after treatment has ended).

Search methods for identification of studies

See the 'Specialized register' section in the Cochrane Stroke Group module. We will search for trials in all languages and arrange for the translation of relevant articles where necessary.

Electronic searches

We will search the Cochrane Stroke Group trials register and the following electronic databases from their inception.

- The Cochrane Central Register of Controlled Trials (CENTRAL) (in the Cochrane Library, latest issue);
- MEDLINE (from 1946) (EBSCO) (Appendix 1);
- Embase (from 1980) (Ovid);
- CINAHL (from 1937) (EBSCO);
- AMED (from 1985) (EBSCO);
- PsycINFO (from 1987) (EBSCO);
- Open Grey (www.opengrey.eu/);
- OTSeeker (www.otseeker.com/);
- PEDro: Physiotherapy Evidence Database (www.pedro.org.au);
- REHABDATA (National Rehabilitation Information Centre) (www.naric.com/?q=REHABDATA);
- ProQuest Dissertations & Theses (www.proquest.com/);
- CIRRIE (cirrie.buffalo.edu/database/).

We developed the MEDLINE search strategy (Appendix 1) with the help of the Cochrane Stroke Group Information Specialist and will adapt it for the other databases. We will search for all relevant RCTs regardless of language or publication status (published, unpublished, in press or in progress).

We will also search the following trials registers:

- ClinicalTrials.gov (www.clinicaltrials.gov/);
- Stroke Trials Registry (www.strokecenter.org/trials/);
- EU Clinical Trials Register (www.clinicaltrialsregister.eu);
- ISRCTN Registry (www.isrctn.com/);
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) portal (www.who.int/ictrp/en/);
- Australian New Zealand Clinical Trials Registry (www.anzctr.org.au/);
- UK Clinical Trials Gateway (www.ukctg.nihr.ac.uk).

Searching other resources

We will handsearch the reference lists of all identified studies and systematic reviews for any further potentially eligible studies and handsearch any relevant journals or conference proceedings that have not already been identified by the Cochrane Stroke Group. In addition, we will contact key authors and organisations to obtain any missing or additional trial data.

We will also undertake reference searching using Web of Science Citation Indexes for all included studies for further references to relevant trials.

Data collection and analysis

Selection of studies

We will collate the search results using bibliographic software and will remove duplicates prior to screening. Two review authors (BC and JB) will independently screen titles and abstracts of the studies retrieved via the searching process. We will exclude those studies that are obviously irrelevant. We will retrieve the full-text articles for the remaining references and two review authors (BC and JW) will independently screen the full-text articles and identify studies for inclusion, and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreements through discussion and, if required, we will consult a third author (JB). We will collate multiple reports of the same study, to ensure that no single study is duplicated in reporting. We will record the selection process and complete a PRISMA flow diagram (Moher 2009) and will complete tables of 'Characteristics of included studies' and 'Characteristics of excluded studies'.

Data extraction and management

Two review authors (of BC, JB and JW), working independently, will extract data from each study. We will use the "template for intervention description and replication" (TIDieR) checklist and guide (Hoffmann 2014) to extract data from studies identified as eligible for inclusion. In addition to the 12 points on the TIDierR checklist, we will also include information on study eligibility, the study participants, the outcomes measured (including time points) and a 'miscellaneous' section (which may include funding sources, key conclusions from the study authors, references to other relevant studies, correspondence required, and any other comments by the review author). We will include detailed information on time spent in rehabilitation in section 8 of the TIDieR checklist, entitled 'When and how much'. Prior to commencing data extraction, we will pilot the adapted TIDieR checklist to ensure the tool is extracting the data required and that review authors are using the tool comparably.

If there are any discrepancies in the data extraction, the two review authors who have extracted the data will initially try to resolve them via discussion, with involvement of the third review author where resolution cannot be achieved.

Assessment of risk of bias in included studies

Two review authors (BC and JW) will independently assess risk of bias for each study using Cochrane's tool for assessing risk of bias (Higgins 2011). We will resolve any disagreements by discussion or by involving another review author (JB). We will assess the risk of bias according to the following domains.

- Random sequence generation (selection bias)
- Allocation concealment (selection bias)
- Blinding of participants and personnel (performance bias)
- Blinding of outcome assessment (detection bias)
- Incomplete outcome data (attrition bias)
- Selective outcome reporting (reporting bias)
- Other bias

Examples of possible sources of bias are non-comparable co-interventions between intervention and control groups, baseline imbalances between groups, and deviation from study protocol. We will grade each bias, if identified, using the criteria provided in table 8.5.d of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). We will grade risk of bias for each domain as high, low or unclear and we will give a justification for the grading in the 'Risk of bias' tables. If cluster-randomised trials are included, we will assess their risk of bias using the same method, but paying particular attention to the risk of bias particular to these types of studies (Higgins 2011b).

We will summarise the risk of bias for each individual study, using 'Risk of bias' summary and across studies using a 'Risk of bias' graph. The assessment of risk of bias of blinding of outcome assessment will be dependent on the potential influence that lack of blinding may have. If the outcome assessor is not blinded and we judge that the outcome measure could be influenced by the assessor, we will assign a high risk of bias. If we judge that the outcome measure could not be influenced by the assessor, we will assign a low risk of bias, regardless of whether or not the outcome assessor was blinded.

We will consider incomplete outcome data reporting in terms of outcome data missing immediately to two weeks post completion of treatment and outcome data missing to medium-/long-term follow-up.

Review authors will not assess the risk of bias for studies in which they were involved.

Measures of treatment effect

In order to address the first objective of this review, we will undertake statistical analyses using Review Manager 5 (RevMan 5) (RevMan 2014). For continuous outcomes using different scales of measurement, we will calculate pooled standardised mean difference (SMDs) and 95% confidence intervals (CIs). We will express dichotomous outcomes as risk ratios (RR) with 95% CIs.

In order to address the second objective of this review, we propose treating the difference between arms, in terms of amount of rehabilitation, as a continuous study-level characteristic whose effect on estimated treatment effect we will also investigate using meta-regression. Based on the advice in chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011), should there be fewer than 10 studies, we will not undertake a meta-regression; we will instead conduct a subgroup analysis descriptively comparing studies with a large difference between arms (in terms of amount of rehabilitation) and those with a small difference between arms. We will use a median split based on differences in amount of time spent in rehabilitation between arms to determine the subgroups. Descriptive analysis will comprise scatter plots of differences in amount of time spent in rehabilitation (i.e. number of minutes of rehabilitation, frequency of rehabilitation) against estimated treatment effect. This will enable a simple visual inspection of whether estimated treatment effect varies with differences in amount of time spent in rehabilitation.

To address the third objective of this review, we will group together studies in which the rehabilitation schedule was similar in terms of:

- average minutes of rehabilitation provided per week;
- average frequency of rehabilitation provided per week (i.e. number of days per week on which rehabilitation was provided);
- total duration of rehabilitation.

We will undertake meta-analyses for the different groups. For continuous outcomes using different scales of measurement, we will calculate pooled SMDs and 95% CIs. We will express dichotomous outcomes as RRs with 95% CIs. We will then compare the outcomes of these analyses to determine if they identify certain traits of the rehabilitation schedule, which may lead to better outcomes.

Unit of analysis issues

We will consider unit of analysis issues in the inclusion of cluster-randomised trials. If cluster-randomised trials have been analysed taking into account the intra-class correlation, we will be able to synthesis these with other studies. The intra-class correlation is an estimation of the variability within clusters and between clusters (Higgins 2011b).

If cluster-randomised trials have not been appropriately analysed, taking into account the intra-class correlation, then we will establish if relevant information required to derive suitable estimates is provided (following the guidance in section 16.3.4 of the *Cochrane Handbook for Systematic Reviews of Interventions,* Higgins 2011b). If we are not able to derive suitable estimates, then we will exclude the study from the synthesis.

We will perform a sensitivity analysis to determine the effect of including cluster-randomised trials in the review.

Dealing with missing data

We will contact study authors to obtain any outcome data missing from the included studies. If it is not possible to obtain missing data, we will aim to at least determine the reason for missing data from study authors, in order to determine if data are 'missing at random' or 'missing not at random'.

If data are 'missing at random', we will analyse the available data and ignore missing data. If data are 'missing not at random', then we will impute the last observation carried forward. We will conduct a sensitivity analysis to determine the effect of missing data. We will discuss the potential impact of missing data in the review.

Assessment of heterogeneity

We will visually inspect the forest plots to determine the overlap in the CIs of the studies. Poor overlap is like to indicate statistical heterogeneity (Deeks 2011). In addition, we will use the I^2 statistic to quantify heterogeneity in the study results (Higgins 2003). If the I^2 result is greater than 50%, we will consider this to represent substantial heterogeneity (Deeks 2011).

If we find substantial heterogeneity, we will explore the possible reasons for this by examining the trials in terms of their design, risk of bias, clinical settings, interventions, and participants involved. We will analyse possible sources of heterogeneity by undertaking the proposed subgroup analyses and explore the effect of potential bias by undertaking the subgroup analyses proposed.

Assessment of reporting biases

We will attempt to minimise the effect of reporting bias by using a comprehensive search strategy. We will use funnel plots of the primary and secondary outcomes to provide a visual inspection of whether treatment estimates are associated with the study size (Sterne 2011).

Data synthesis

We will not undertake data synthesis if studies are clinically diverse or demonstrate high levels of bias across all important domains. Where we consider studies to be sufficiently similar, we will conduct meta-analyses by pooling the appropriate data using RevMan 5 (RevMan 2014) following the guidance provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). One author (BC) will enter the data into RevMan 5 and a second author (SE) will check the accuracy of this. We will resolve disagreements through discussion.

We will use a random-effects meta-analysis (DerSimonian 2015), regardless of the level of heterogeneity between studies. If the studies are heterogeneous, then this is the appropriate model to use. However, if heterogeneity is low, a random-effects model will return very similar results to a fixed-effect model.

Provided enough studies are identified, we will undertake a meta-regression by pooling the appropriate data using RevMan 5 (RevMan 2014). The *Cochrane Handbook for Systematic Reviews of Interventions* states that meta-regression should not be considered if there are fewer than 10 studies in a meta-analysis (Deeks 2011). We will use a random-effects meta-regression (Thompson 2002), utilising the 'metareg' macro for the Stata statistical package (www.stata.com). One author (BC) will enter the data into Stata and a second author (SE) will check the accuracy of this. We will resolve disagreements through discussion.

GRADE and 'Summary of findings' table

We will create 'Summary of findings' tables to present the findings of our first objective, using the seven outcomes identified: ADL, activity measures of the upper limb, activity measures of the lower limb, motor impairment measures of the upper limb, motor impairment measures of the lower limb, serious adverse events/death, and participant experience.

We anticipate using three tables, to summarise the findings of the data synthesis as follows.

- Greater time spent in rehabilitation versus lesser time spent in rehabilitation after stroke (outcomes immediately after intervention).
- Greater time spent in rehabilitation versus lesser time spent in rehabilitation after stroke (outcomes from two weeks to six months after intervention).
- Greater time spent in rehabilitation versus lesser time spent in rehabilitation after stroke (outcomes after six months after intervention).

For each outcome, we will report the number of participants that contribute to the finding, the relative effect, direction of effect and the quality of the evidence. Please see Table 1 for the template of the 'Summary of findings' table we will use.
We will analyse the quality of the evidence using the evidence grading system developed by the GRADE collaboration (GRADE 2013), using the methods described in section 12.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011).

Subgroup analysis and investigation of heterogeneity

Where studies have provided the necessary information, we will stratify the studies to analyse possible sources of heterogeneity using the following characteristics.

- Studies in which the experimental group has received five hours or more of rehabilitation per week.
- Studies in which the experimental group has received 10 hours or more of rehabilitation per week.
- Studies in which the experimental group has received 20 hours or more of rehabilitation per week.
- Studies in which the experimental group has received 30 hours or more of rehabilitation per week.
- Studies in which the rehabilitation has been provided within the first six months after stroke.
- Studies in which the rehabilitation has been provided after six months after stroke.

We require studies to provide clear indication of the time spent in therapy per week and the time post-stroke that intervention was provided, in order to undertake this analysis.

Sensitivity analysis

We will perform a sensitivity analysis by descriptively comparing the results of two meta-analyses that either include or exclude studies that meet at least one of the following criteria:

- no description of randomisation;
- no description of concealed allocation, or no concealment used;
- no description of blinding of outcome assessors, or no blinding of outcome assessors used, where outcome measurement could have been influenced by the assessor;
- unclear or inadequate approaches of dealing with missing data (including studies in which we have been required to impute missing data);
- Inclusion of cluster-randomised trials.

We have chosen these criteria as being important markers of potential sources of bias.

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* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. Template 'Summary of findings' table

Outcome	No. of studies/participants	Relative effect (95% CI)	Direction of effect	Quality of evidence/ GRADE	Comments
Activities of daily living					
Activity measures of the upper limb					
Activity measures of the lower limb					
Motor impairment measures of the upper limb					
Motor impairment measures of the lower limb					
Serious adverse events/death					
Participant experience					

APPENDICES

Appendix 1. MEDLINE search strategy

We will use the following strategy for MEDLINE and will modify it, as appropriate, to suit other databases.
1. cerebrovascular disorders/ or exp basal ganglia cerebrovascular disease/ or exp brain ischemia/ or exp carotid artery diseases/ or exp intracranial arterial diseases/ or exp "intracranial embolism and thrombosis"/ or exp intracranial hemorrhages/ or stroke/ or exp brain infarction/ or stroke, lacunar/ or vasospasm, intracranial/ or vertebral artery dissection/
2. (stroke or poststroke or post-stroke or cerebrovasc$ or brain vasc$ or cerebral vasc$ or cva$ or apoplex$ or SAH).tw.
3. ((brain$ or cerebr$ or cerebell$ or intracran$ or intracerebral) adj5 (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$)).tw.
4. ((brain$ or cerebr$ or cerebell$ or intracerebral or intracranial or subarachnoid) adj5 (haemorrhage$ or hemorrhage$ or haematoma$ or hematoma$ or bleed$)).tw.
5. hemiplegia/ or exp paresis/
6. (hemipleg$ or hemipar$ or paresis or paretic).tw.
7. 1 or 2 or 3 or 4 or 5 or 6
8. physical therapy modalities/ or physical therapy specialty/ or exp exercise movement techniques/ or exp exercise therapy/ or hydrotherapy/ or kinesiology, applied/

9. “Physical and Rehabilitation Medicine”/
10. rehabilitation/ or “activities of daily living”/ or occupational therapy/ or recreation therapy/ or rehabilitation, vocational/ or “Recovery of Function”/
11. movement/ or motor activity/ or exercise/ or circuit-based exercise/ or cool-down exercise/ or muscle stretching exercises/ or physical conditioning, human/ or plyometric exercise/ or resistance training/ or exp running/ or swimming/ or walking/ or warm-up exercise/ or exercise test/
12. exp sports/
13. physical exertion/ or exp physical endurance/ or physical fitness/
14. muscle stretching exercises/ or resistance training/
15. muscle contraction/ or isometric contraction/ or isotonic contraction/
16. (physiotherap$ or (physical adj3 (mobilis$ or mobiliz$ or exercise$ or exertion or endurance or therap$ or conditioning or activit$ or fitness))).tw.
17. (rehabilitation or recovery of function or exercise$ or mobilis$ or mobiliz$ or motion therap$ or motor activit$ or motor skill$ or activities of daily living or adl or manipulat$ or (occupational adj3 (train$ or rehab$ or therap$ or activit$ or regim$))).tw.
18. (exercise adj3 (train$ or intervention$ or protocol$ or program$ or therap$ or activit$ or regim$)).tw.
19. (fitness adj3 (train$ or intervention$ or protocol$ or program$ or therap$ or activit$ or regim$ or centre$ or center$)).tw.
20. ((training or conditioning) adj3 (intervention$ or protocol$ or program$ or activit$ or regim$)).tw.
21. (sport$ or recreation$ or leisure or cycling or bicycl$ or rowing or treadmill$ or running or circuit training or swim$ or walk$ or dance$ or dancing or tai ji or tai chi or yoga).tw.
22. ((endurance or aerobic or cardio$) adj3 (fitness or train$ or intervention$ or protocol$ or program$ or therap$ or activit$ or regim$)).tw.
23. (muscle strengthening or progressive resist$).tw.
24. ((weight or strength$ or resistance) adj3 (train$ or lift$ or exercise$)).tw.
25. ((isometric or isotonic or eccentric or concentric) adj3 (action$ or contraction$ or exercise$)).tw.
26. or/8-25
27. cerebrovascular disorders/rh or exp basal ganglia cerebrovascular disease/rh or exp brain ischemia/rh or exp carotid artery diseases/rh or cerebrovascular accident/rh or exp brain infarction/rh or exp cerebrovascular trauma/rh or exp hypoxia-ischemia, brain/rh or exp intracranial arterial diseases/rh or intracranial arteriovenous malformations/rh or exp “intracranial embolism and thrombosis”/rh or exp intracranial hemorrhages/rh or vasospasm, intracranial/rh or vertebral artery dissection/rh or (hemiplegia/rh or exp paresis/rh)
28. (intensive or intensity or augment$ or accelerate$ or additional or dosage or dose-response or frequency or amount or quantity).tw.
29. 27 and 28
30. 7 and 26 and 28
31. 29 or 30
32. Randomized Controlled Trials as Topic/
33. random allocation/
34. Controlled Clinical Trials as Topic/
35. control groups/
36. clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/
37. double-blind method/
38. single-blind method/
39. Therapies, Investigational/
40. Research Design/
41. randomized controlled trial.pt.
42. controlled clinical trial.pt.
43. clinical trial.pt.
44. random$.tw.
45. (controlled adj5 (trial$ or stud$)).tw.
46. (clinical$ adj5 trial$).tw.
47. ((control or treatment or experiment$ or intervention or surgical) adj5 (group$ or subject$ or patient$)).tw.
48. (quasi-random$ or quasi random$ or pseudo-random$ or pseudo random$).tw.
49. ((control or experiment$ or conservative) adj5 (treatment or therapy or procedure or manage$)).tw.
50. ((singl$ or doubl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).tw.

51. (coin adj5 (flip or flipped or toss$)).tw.
52. latin square.tw.
53. versus.tw.
54. controls.tw.
55. or/32-54
56. 31 and 55

CONTRIBUTIONS OF AUTHORS

All authors contributed to the conception and design of the review and approved the draft protocol. All authors will be involved at all stages of the review.

BC, JB and JW will screen titles and abstracts of publications identified by the searches.

BC, JB, JW and SE will extract trial and outcome data from the selected trials and analyse outcome data.

BC, JW and JB will be involved in assessing risk of bias in the included studies.

All review authors will interpret the results.

DECLARATIONS OF INTEREST

BC: Funding from Health Education Wessex, Poole Hospital NHS Foundation trust and the Elizabeth Casson Trust in order to pay tuition fees for Part Time Doctorate in Clinical Practice (undertaken at the University of Southampton). Employed full-time by Poole Hospital NHS Foundation Trust

JW: none known

JB: none known

GK: none known

JM: none known

SE: none known

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